

MATH 598 - PROJECT 3

Please submit your project by 11.59 pm on 5th April by uploading a single pdf to myCourses.

A one-compartment pharmacokinetic (PK) model for the amount of drug in the bloodstream, $y(x)$, of an individual at time x after an initial dose of size D at time $x = 0$ takes the form

$$y(x) = D\alpha \exp\{-\lambda x\} = \mu(x; \alpha, \lambda, D) \quad x > 0$$

for parameters $\alpha_1, \alpha_2, \lambda_1, \lambda_2 > 0$. This model represents simple exponential decay of the amount of drug. A typical model used for representing data collected in PK studies is to use a multiplicative error structure such that

$$\log y(x) = \log \mu(x; \alpha, \lambda, D) + \epsilon$$

where $\epsilon \sim \text{Normal}(0, \sigma^2)$ represents a random observation error that is independent and identically distributed across all observations.

Due to the positivity constraints on the parameters, a reparameterization $\theta_1 = \log \alpha$ and $\theta_2 = \log \lambda$ is often used for statistical inference.

- (a) Using the above model, and a Normal-Inverse Gamma prior distribution for the three parameters $(\theta_1, \theta_2, \sigma^2)$, perform a Bayesian analysis using MCMC of the following data which represent observations on a single individual.

x	0.50	1.00	1.50	2.00	2.50	3.00	3.50	4.00	4.50	5.00	5.50	6.00
y	268.94	133.73	75.35	52.40	26.47	26.52	13.69	13.05	5.02	2.14	2.26	0.75

You may choose any suitable **proper** Normal-Inverse Gamma prior distribution. Summarize the posterior inference, and demonstrate the adequacy of your MCMC approach. 12 MARKS.

- (b) In a population PK study, data from m individuals are collected, where it is considered that the PK parameters for each individual are different, thereby necessitating a hierarchical model: if $i = 1, \dots, m$ indexes individuals in the study, and $j = 1, \dots, n$ indexes the observation on an individual, then

- **STAGE 1: Observed data:**

$$\log Y_{ij} \sim \text{Normal}(\log \mu(x_{ij}; \theta_{i1}, \theta_{i2}, D), \sigma^2) \quad i = 1, \dots, m, j = 1, \dots, n \text{ independently}$$

- **STAGE 2: Population model:**

$$(\theta_{i1}, \theta_{i2}) \sim \text{Normal}_2(\mu, \Sigma) \quad i = 1, \dots, m \text{ independently}$$

where $\mu \in \mathbb{R}^2$ and Σ is a 2×2 positive definite matrix.

- **STAGE 3: Prior model:** the prior model in this case is the **Normal-Inverse Wishart** model which assumes that

$$\Sigma \sim \text{InverseWishart}(\nu, \Psi)$$

$$\mu | \Sigma \sim \text{Normal}_2(\eta, \Sigma/\lambda)$$

where $\eta \in \mathbb{R}^2$, $\nu > 1$ is a scalar and Ψ is a 2×2 positive definite matrix. This prior is explained in more detail below.

Using MCMC, carry out a Bayesian analysis of the data in the file `PK1example.csv` using this population PK model where the dose value is $D = 100$: here the x values are measured in hours, and there are $n = 12$ measurements made at half hour intervals for each of the $m = 15$ individuals in the study. Summarize the posterior inference for first stage and second stage models, and demonstrate the good performance of your algorithm.

18 MARKS.

Note: You may adapt code from the `knitr` files provided for the course.

The Normal-Inverse Wishart (NIW) Prior

This prior is the standard conjugate prior for multivariate Normal problems. The Inverse Wishart prior is a conjugate prior for $d \times d$ covariance matrices. It has two hyperparameters:

- ν (a degrees of freedom parameter) which is a real-valued scalar such that $\nu > d - 1$;
- Ψ is a positive definite $d \times d$ “precision” matrix.

The prior for Σ takes the form

$$\pi_0(\Sigma) \propto |\Sigma|^{-(\nu+d+1)/2} \exp \left\{ -\frac{1}{2} \text{Tr}(\Psi \Sigma^{-1}) \right\}$$

where Tr is the trace function (that is, for square matrix $\mathbf{A}$, $\text{Tr}(\mathbf{A})$ returns the sum of the diagonals of the matrix). The expected value of this distribution is the matrix

$$\frac{1}{\nu - d - 1} \Psi$$

provided $\nu > d + 1$.

The most common use of this prior is for multivariate data $\mathbf{y}_1, \dots, \mathbf{y}_n$ arising from the model

$$\mathbf{Y}_i | \mu, \Sigma \sim \text{Normal}_d(\mu, \Sigma) \quad i = 1, \dots, n \text{ independently.}$$

For such data, the $NIW(\eta, \lambda, \nu, \Psi)$ prior is conjugate to the corresponding likelihood, and the posterior distribution is then $NIW(\mu_n, \lambda_n, \nu_n, \Psi_n)$ where

$$\eta_n = \frac{n\bar{\mathbf{y}} + \lambda\eta}{n + \lambda} \quad \lambda_n = n + \lambda \quad \nu_n = n + \nu$$

and

$$\Psi_n = \sum_{i=1}^n (\mathbf{y}_i - \bar{\mathbf{y}})(\mathbf{y}_i - \bar{\mathbf{y}})^\top + \frac{n\lambda}{n + \lambda} (\bar{\mathbf{y}} - \eta)(\bar{\mathbf{y}} - \eta)^\top + \Psi$$

where

$$\bar{\mathbf{y}} = \frac{1}{n} \sum_{i=1}^n \mathbf{y}_i$$

and η, ν and Ψ are hyperparameters. Thus

$$\pi_n(\mu | \Sigma) \equiv \text{Normal}(\eta_n, \Sigma / \lambda_n) \quad \pi_n(\Sigma) \equiv \text{InverseWishart}(\nu_n, \Psi_n).$$

These results are the multivariate analogue of the earlier univariate result. The Inverse Wishart distribution can be regarded as a multivariate analogue of the Inverse Gamma distribution.

In R, sampling from the Inverse Wishart distribution is easily achieved using (for example) the `riwish` function from the `MCMCpack` library